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# Control of pain with topical plant medicines

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PEER REVIEW

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ABSTRACT

Pain is normally treated with oral nonsteroidal anti-inflammatory agents and opioids. These drugs are dangerous and are responsible for many hospitalizations and deaths. It is much safer to use topical preparations made from plants to treat pain, even severe pain. Topical preparations must contain compounds that penetrate the skin, inhibit pain receptors such as transient receptor potential cation channels and cyclooxygenase-2, to relieve pain. Inhibition of pain in the skin disrupts the pain cycle and avoids exposure of internal organs to large amounts of toxic compounds. Use of topical pain relievers has the potential to save many lives, decrease medical costs and improve therapy.

## 1. Introduction

Pain can be difficult to treat, especially chronic pain. Fibromyalgia, neuropathic pain and chronic back pain are routinely treated with oral opioids, such as hydrocodone and oxycodone. A recent systematic review found no convincing evidence that oxycodone is of value in pain treatment from fibromyalgia, diabetic neuropathy, postherpetic neuralgia or neuropathic pain[1]. Osteoarthritis pain is frequently treated with oral nonsteroidal anti-inflammatory drugs (NSAIDs). When the NSAIDs are inadequate for pain control in osteoarthritis or rheumatoid arthritis, stronger agents are used such as corticosteroids, hydroxychloroquine, sulfasalazine, leflunomide, auranofin, etanercept, infliximab, anakinra and methotrexate. This is called the Carpenter approach[2]. If the hammer does not work, get a bigger hammer. All of these agents have serious adverse effects. Methotrexate can kill patients if an excessive dose is used.

Of course, NSAIDs were discovered based on the structure of aspirin, a monoterpenoid, which comes from meadowsweet, *Filipendula ulmaria*. Opioids are alkaloids that come from the opium poppy, *Papaver somniferum*. The problem with these agents is that large doses are taken orally or by injection, travel throughout the body and have toxic effects where they are not needed. NSAIDs are used in chronic pain conditions, but are not effective for most patients[3]. NSAIDs cause 100 000 ulcers in the USA every year according to the Centers for Disease Control. Of these, 10 000 patients die. NSAIDs also damage the kidneys and have other adverse effects. Opioids cause seizures and respiratory depression. They cause 14 000 deaths every year in the USA according to the Centers for Disease Control. They also cause addiction and tolerance such that after a couple of weeks, patients have to increase the dose to get any pain relief.

This review will point out that there is a better way to treat pain than by giving large oral doses or injections to treat pain in the brain and brain stem. Liniments and other topical preparations can be used that are applied in small amounts to the skin where they are needed. Analgesic molecules in the preparations penetrate the skin in small but sufficient amounts, act where they are needed and are rapidly cleared from the skin and the body.

## 2. What is the pain cycle

There is a pain cycle in the body that starts with pain receptors on

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sensory afferent neurons of the skin. These are small unmyelinated (C-type) or thinly myelinated (A delta-type) nerves. The sensory afferents have a pseudo-unipolar morphology[4]. A common axonal stalk sends axons to the skin and to the brain stem where they synapse with ascending neurons that communicate with the hippocampus, hypothalamus and other brain regions. This pseudo-unipolar morphology may be important in reflex amplification of the pain cycle. The brain neurons communicate with descending neurons that synapse with neurons in the brain stem. These descending brain stem neurons have terminals in the skin that are neurotrophin secreting[5]. Activation of the pain cycle can magnify pain in the body.

Sensory afferent neurons contain a number of different pain receptors. These pain receptors are activated or inhibited by various natural substances such as histamine that are made in the skin, work in the skin, and do not persist for very long in the skin.

These neurons are also regulated by input from the brain stem and the brain. The most abundant pain receptors in the skin are located on sensory afferent neurons and are called transient receptor potential (TRP) cation channels. These channels are usually made up of six membrane spanning units and a central cation permeable channel. Some TRP channels are also located in the brain and the brain stem. These receptors form a family of receptors that respond to heat, cold, mechanical stress and other painful stimuli. TRP channels have a characteristic of opening in response to an agonist, which then results in inhibition. In other words, agonists and antagonists can have the same long term effects, pain inhibition. TRP channels are not all expressed in the same skin afferent neurons. There are distinct neuronal populations that express the various TRP channels[4]. It is convenient to describe these receptors in terms of the agonists and antagonists that interact with them.

The canonical TRP subfamily TRPC, has at least 7 members[6], which tend to be activated by diacylglycerol. Phospholipase C makes diacylglycerol, which is an endogenous compound.

The vanilloid subfamily, TRPV, has 6 members and tends to be activated by heat[6]. However, TRPV4 can be activated by swelling caused by 5',6'-epoxyeicosatetrienoic acid, an endogenous compound. Capsaicin is an agonist for TRPV1. Activation of the channel by capsaicin causes pain, results in later inactivation of the channel and relief of pain. Eugenol and gingerol are monoterpenoid agonists for TRPV1[7]. This channel is activated by endovanilloids, cannabinoids, endocannabinoids, hydroperoxyeicosatetraenoic acid (HPETE), hydroxyeicosatetraenoic acid (HETE) and other compounds[6]. Endovanilloids, endocannabinoids, HPETE and HETE are made in the skin, act in the skin and are quickly cleared from the skin. Bradykinin and ATP sensitize TRPV1 by stimulating protein kinase $C_\varepsilon$ dependent phosphorylation to greatly increase pain[8]. Lidocaine activates TRPV1, whereas isoflurane, enflurane, sevoflurane and desflurane sensitize TRPV1 can increase pain[7]. Dynorphins and adenosine are TRPV1 antagonists in the brain[7]. Histamine and several prostaglandins potentiate the activity of TRPV1, greatly increasing pain and itch[9]. TRPV2 is activated, then inhibited, by cannabidiol and tetrahydrocannabinol[7]. The monoterpenoid, citral, inhibits TRPV2[7]. TRPV3 is activated by camphor, thymol, eugenol, carveol, carvacrol, borneol, menthol, and all plant-derived monoterpenoids[6,10]. TRPV4 is activated by endocannabinoids, arachidonic acid metabolites, the diterpenoid bisandrographolide A, and is inhibited by the monoterpenoid citral[7]. TRPV5 and TRPV6 are less well characterized. TRPV5 can be inhibited by econazole[7].

The melastatin subfamily, TRPM, has several members[6]. TRPM1 is activated by steroids[9]. The TRPM2 receptor is activated by ADP-ribose, cyclic ADP-ribose, hydrogen peroxide and heat[6]. The TRPM3 receptor is activated by sphingosine. TRPM4 and 5 are activated by heat. TRPM8 is activated by cold, menthol and icilin. ADP-ribose, cyclic ADP-ribose, hydrogen peroxide and sphingosine are endogenous compounds that are made in the skin, act in the skin and can be quickly cleared from the skin.

The ankyrin subfamily, TRPA, has one member. TRPA1 responds to allicin, isothiocyanates, cannabinoids, cinnamaldehyde and arachidonic acid[6]. Arachidonic acid is an endogenous compound that is made in the skin, acts in the skin and is quickly cleared from the skin. The A and J series of prostaglandins activate the channel[9]. TRPA1 also responds to methyl salicylate, isoflurane and lidocaine[4,7].

The polycystin subfamily, TRPP, has three members[6]. They tend to respond to mechanical stress and calcium. The mucolipin subfamily TRPML has three members[6]. This family is not well characterized, appears to be located on lysosomal membranes and may respond to protons.

All TRP channels are calcium channels[6]. Some are permeable to other cations as well such as $Na^+$ and $Mg^{2+}$. If TRP channels open too much, excessive calcium may enter the sensory nerve terminal and activate apoptosis mechanisms[11]. This apoptosis is an essential component of pain control. The nearby nerve growth factor secreting efferent terminals may facilitate the recovery of the apoptotic afferent terminals.

Cannabinoids and endocannabinoids interact with cannabinoid receptors (CB) CB1 and CB2 to induce peripheral and central pain sensitization[12]. The endocannabinoids are endogenous, made locally, act locally and have short half lives. These compounds include 2-arachidonyl glycerol and anandamide. They also act on TRP channels as discussed above.

Lipoxins are endogenous compounds made from arachidonic acid and interact with ALX receptors (ALX/formyl peptide receptor 2, lipoxin $A_4$ receptor, resolvin D1 receptor) to cause pain. They are made locally, act quickly and do not persist in the skin. Lipoxins exist in a balance with resolvins, which are also made from arachidonic acid and relieve pain[13]. Resolvins interact with a number of receptors including ALX, GPR32 (G protein coupled receptor 32, resolvin D1 receptor, lipoxin $A_4$ receptor), ChemR23 (CMKLR1, chemokine like receptor 1, resolvin E1 receptor) and leukotriene B(4) receptor (BLT1). Resolvins also inhibit TRPA1, TRPV3 and TRPV4 to stop the pain cycle[14].

Opioid receptors are involved in processing pain centrally. The μ, δ, κ and nociceptin receptors are important in pain control,

tolerance and addiction[15]. Current therapy with oral opioids targets brain and spinal cord receptors. However, μ, δ and κ receptors are also found on peripheral sensory neurons. The brain and spinal cord receptors bind to endogenous opioid peptides such as the endorphins, enkephalins, dynorphins and nociceptin. These peptides are produced in a balance in the brain to control pain. However, administration of large doses of oral opioids throws off this balance. Whereas enkephalins and endorphins usually cause analgesia, dynorphins and nociceptin can cause pain sometimes. Chronic use of oral opioids can cause an increase in pain, opioid hyperalgesia. As some opioid receptors become tolerant to agonist actions, other opioid receptors may have breaks in tolerance. Nociceptin may be involved in opioid hyperalgesia[16].

There are many other receptors involved in the pain cycle: bradykinin receptors B1 and B2, serotonin (5-HT) receptors 5-$HT_{1B}$ and 5-$HT_3$, ATP receptors $P2X_3$ and $P2X_4$, N-type calcium channels, voltage gated sodium channels, glutamatergic receptors and others[8]. Prostaglandin E receptors (EP) EP1, EP2, EP3C and EP4 also cause pain in the pain cycle[17]. Some of these receptors can be induced to augment the pain cycle. The B1 receptor is induced by tissue damage, tumor necrosis factor $\alpha$ and interleukin-1$\beta$. Prostaglandins act on dorsal horn neurons to increase central sensitization. prostaglandin $E_2$ ($PGE_2$) and 5-HT activate voltage gated sodium channel type v1.8 receptors to increase pain. Prostaglandins also stimulate cyclic adenosine monophosphate production in sensory neurons and facilitate pain[18]. Histamine receptors $H_1$, $H_3$ and $H_4$ are in the skin and are involved in pain and vasodilation[19,20].

Several endogenous compounds facilitate the pain cycle at TRPV1, such as the prostaglandins prostacyclin and $PGE_2$. Bradykinin and ATP bind to their own receptors which enhances pain sensation at TRPV1 channels[4]. Serotonin and histamine are released by mast cells and potentiate the activation of TRPV1[7,9]. 4-Hydroxy-2-nonenal, hydrogen peroxide, hydrogen sulfide and other endogenous compounds facilitate the activation of TRPA1 channels to greatly increase pain[4].

Drug therapy with NSAIDs can have disastrous long term effects in chronic pain patients. By inhibition of cyclooxygenase enzymes, the balance of endogenous pain causing and pain relieving compounds is altered. Lipoxins cause pain. Resolvins relieve pain. Prostaglandins cause and enhance pain. When NSAIDs are used chronically, the balance between these arachidonic acid derived compounds is lost. Pain management does not occur. Clotting and other NSAID toxicity problems predominate. Another problem with NSAIDs is that oral doses do not penetrate into the skin adequately to inhibit skin cyclooxygenase enzymes. Application of NSAIDs onto the skin or into the skin provides better pain relief[21].

## 3. Why is the incidence of painful conditions increasing

Pain is an increasing clinical problem for two main reasons: the incidence of arthritis is increasing and patients want to be treated with opioids. Drug seeking behavior has become common, especially for hydrocodone and oxycodone. These drugs cause addiction and tolerance such that the dose is increased until toxicity occurs. Arthritis is increasing due to the increase in obesity[22]. The Centers for Disease Control have published statistics on their website that demonstrate the increase in arthritis incidence over the past 20 years or so. Polynesians experience 1.5 times more incidence in arthritis than other groups.

Visceral fat increases during obesity, especially in adults. Visceral fat secretes inflammatory adipokines that damage cartilage and bone resulting in pain and osteoporosis[22]. Toxic lipids, such as ceramide and the endocannabinoids, increase in visceral fat obesity. Endocannabinoids increase the secretion of inflammatory adipokines by visceral fat. Tumor necrosis factor $\alpha$, resistin, colony stimulating factor-1, leptin and visfatin are inflammatory adipokines involved in causing inflammation of the joints by stimulation of macrophages, T cells and neutrophils. Macrophages become osteoclasts and break down bone. Even chondrocytes are stimulated to break down cartilage.

Patients should be taught to alter their lifestyles in order to prevent arthritis. This is by far the safest and least expensive way to deal with arthritis. Traditional concepts such as living in balance can be taught to patients to help them alter their lifestyles[23].

## 4. How is cyclooxygenase-2 involved in chronic pain

Cyclooxygenase-2 is induced in the skin and other sites during chronic pain[21]. Cyclooxygenase-2 is the major source of prostaglandins in the body. Prostaglandins bind to their own prostaglandin receptors to cause pain and also potentiate the activation of TRPV1 receptors to greatly increase pain. Inhibition of skin cyclooxygenase-2 is very useful in chronic pain therapy. However, oral administration of cyclooxygenase-2 inhibitors does not provide adequate therapy in the skin[21]. It is important to apply cyclooxygenase-2 inhibitors onto the skin to inhibit the enzyme at sites of pain. This allows the use of small amounts of drug and avoids systemic drug toxicity. The current cyclooxygenase-2 inhibitors do not alter the induction of the enzyme during chronic pain. Drugs are needed that down regulate the enzyme to provide recovery from chronic pain conditions.

## 5. Liniment for the control of pain

A powerful pain reliever is produced from California sagebrush, *Artemisia californica*. This is a traditional medicine used by California Indians[24,25]. The liniment is used at painful sites on the skin and provides rapid pain relief that lasts for several hours. The liniment is used in small amounts where it is needed and avoids systemic penetration of large amounts of active compounds. This avoids systemic toxicity problems.

The liniment contains 15 different monoterpenoids[26]. Monoterpenoids in general penetrate the skin easily since they are small, lipophilic compounds. The monoterpenoids inhibit pain at several TRP channels. Camphor, borneol, thujone and eucalyptol inhibit TRPV3[7,10,27]. Camphor also inhibits TRPA1[27]. Eucalyptol

inhibits pain at the TRPM8 receptor and is as potent an analgesic as morphine[4]. Many of the monoterpenoids in the liniment have not been examined to see if they are antinociceptive. It is important for a topical preparation to inhibit as many types of TRP channels as possible since the different TRP channels exist in nonoverlapping populations of sensory nerve terminals. Inhibition of many types of TRP channels may provide the maximum analgesia. It is also possible that a synergism may exist between the various TRP populations of sensory neurons such that inhibition of the outputs from several neurons provides more than additive pain relief.

Many of the monoterpenoids are anti-inflammatory agents. Camphene, borneol and β-pinene inhibit nitric oxide synthase and cyclooxygenase-2 expression through an NF-κB mechanism[28-30]. Not only do these compounds decrease prostaglandin production, they also decrease cyclooxygenase-2 activity at painful sites. This is a major improvement in pain management for chronic pain patients. The liniment also contains the sesquiterpenes leucodin, pestalodiopsolide A, echinolactone B, tanapartholide A and secogorgonolide[26]. These are small, lipophilic compounds that in general can cross the skin. These compounds are anti-inflammatory agents that decrease cyclooxygenase-2 expression[31,32]. A diterpenoid is present in the liniment, xanthohumol disaccharide. It is not known if the disaccharide is cleaved to liberate free xanthohumol in the skin. Xanthohumol inhibits the expression of cyclooxygenase-2[33,34]. This provides another way for the liniment to benefit chronic pain patients.

The liniment also contains flavonoids and alkaloids that are anti-inflammatory[26]. Some flavonoids and alkaloids are known to penetrate the skin and down regulate cyclooxygenase-2. These compounds add to the analgesic and anti-inflammatory effects of the liniment.

The liniment has been used in several hundred patients with success[26]. Patients suffering from broken bones, large abrasions and bruises, spinal stenosis, chronic back pain, fibromyalgia, osteoarthritis, rheumatoid arthritis, cancer pain, bursitis, muscle pain from over exertion, diabetic neuropathy and shingles have been successfully treated. Chronic back pain patients are advised to cut their doses of opioids in half every week while using the liniment. They are also advised to start a daily walking program that involves 20 minutes of gentle, enjoyable walking. Walking clearly helps recovery in many patients. After a few weeks of therapy, many chronic back pain patients report recovery from pain and no further use of opioids.

## 6. Topical preparations for pain control

Black sage, *Salvia mellifera*, is used as a topical preparation to relieve minor to moderate pain[24]. The plant is added to water or sea water. The preparation is placed in sun light for several hours to make a sun tea. Patients soak their feet in the sun tea until pain relief occurs, usually 20 min or so. This traditional preparation is used by patients suffering from arthritis pain, over exertion pain and cramping, headaches, bursitis, minor back pain and other pain.

*Salvia mellifera* contains 54 monoterpenoids that are slightly water soluble, can cross the skin and inhibit pain by inactivating TRP channels[35]. Monoterpenoids have octanol water partition coefficients ranging from 2 for alcohols to 5 for hydrocarbons[36]. This means they are present in water at concentrations ranging from a few ppm to several thousand ppm. Most drugs have octanol water partition coefficients in the range of -0.5 to 4.0. The plant also contains diterpenoids such as rosmanol and carnosic acid that are analgesic and anti-inflammatory agents[37]. Rosmanol is slightly water soluble. Carnosic acid is partly water soluble. These lipophilic molecules may be able to cross the skin and provide pain relief.

Sacred Datura, *Datura wrightii*, is used as a topical preparation to relieve moderate to severe pain[24]. A sun tea made from seven leaves and seven flowers is used. The patient soaks the feet or hands in the preparation until pain relief occurs, usually about 20 min. This traditional preparation is used by patients suffering from abrasions and bruises, arthritis pain, muscle pain from over exertion, moderate back and neck pain, bursitis, gastrointestinal pain, joint pain, foot pain and other types of pain. This topical preparation is safe, effective and has been used by many patients. This is another topical preparation that delivers small amounts of active ingredient to the skin, disrupts the pain cycle and avoids systemic toxicity.

The plant contains the water soluble alkaloids, hyoscyamine and scopolamine. Scopolamine binds to and inhibits all muscarinic receptors. The skin contains muscarinic receptor family (M1, M2, M3, M4 and M5 receptors)[38,39]. Neurons in the skin express M2 receptors[40]. Acetylcholine causes pain in the skin[39,41] by binding to these receptors. Acetylcholine is released by autonomic nerves in the skin, endothelial cells, immune cells and keratinocytes[39,42]. Scopolamine crosses the skin very effectively and inhibits pain. Hyoscyamine and atropine do not efficiently cross the skin. Acetylcholine interacts with TRPV4[43] and TRPV1 channels[44] which may increase pain. It is not known if scopolamine inhibits these interactions. Scopolamine potentiates the analgesic effects of enkephalin and morphine[45] which may have long term effects in pain treatment. Scopolamine is also a very effective antidepressant[46]. It has been known for many years that antidepressants are useful in chronic pain treatment.

*Panax notoginseng*, "san qi" in Chinese, root preparations are used as topical preparations in the treatment of pain[47]. Most of the bioactive components of *Panax notoginseng* are triterpene saponins called ginsenosides[48]. Apparently, ginsenosides can penetrate the skin after topical application[49]. The data show that ginsenoside Rg1 inhibits TRPV1 mediated responses through an NF-kB mechanism that also results in cyclooxygenase-2 down regulation and less $PGE_2$ production[50]. Another study indicates that ginsenosides might directly block TRPV1 channels in sensory neurons[51]. Preparations of this plant have been used for centuries in many patients and are known to be safe.

*Resina Draconis*, dragon's blood, is a red resin from the stem of the tree *Dracaena cochinchinensis*. Flavonoids are the main chemical constituents of the topical preparations[52]. Steroidal saponins are also present[53]. This resinous medicine has anti-bacterial, anti-

spasmodic, anti-inflammatory and analgesic activit[54]. The medicine can be used topically and is very popular in China.

Some flavonoids penetrate the skin[55,56] and decrease the expression of nitric oxide synthase and cyclooxygenase-2, inhibit pain and inflammation[57-59]. Steroidal saponins may cross the skin. Some steroidal saponins are anti-inflammatory[60].

## 7. Conclusions

In general, modern medicine seeks to use drugs that have only one target. For instance, the major pharmacologic activity of celecoxib is inhibition of cyclooxygenase-2 activity. This provides inadequate therapy for many pain patients, because the activity is too specific and because the drug does not get into the skin adequately. It is better to use an analgesic preparation that has many targets, such as inhibition of several TRP channels and down regulation of cyclooxygenase-2. It is better to use an analgesic preparation that is applied to the skin in small amounts. This provides adequate analgesia and avoids systemic toxicity.

Presently, more than 100 000 people in the USA suffer from the toxicity of oral analgesics. Of these, 24 000 people die. Traditional healing teaches that topical preparations are safer and better for pain relief than oral preparations. Many people can be saved from death and suffering by simply switching to topical pain preparations.

## Conflict of interest statement

We declare that we have no conflict of interest.

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